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Case Report

Childhood onset urticaria pigmentosa: A case report from Indonesian setting

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Abstract Urticaria pigmentosa (UP) is a rare skin disease caused by increased deposition of clonal mast cell in the skin. C-kit gene mutation is thought to be the cause of UP. The three components of management include therapeutic aspects, counseling, and avoidance of triggering factors that might activate mast cell degranulation. We reported one case of UP in a 1-year-old boy with a 7-month history of generalized pruritic brownish patches. Dermatological examination revealed generalized hyperpigmented macules, patches and a positive darier's sign. Histopathological examination showed epidermal melanin deposition in the basal layer and mast cell infiltration in the dermal layer which highlighted positively with Giemsa staining. Complete hematology and liver function test were within normal ranges which exclude possibility of internal organ involvement. The initial SCORMA score was 53.4. Patient was treated with a combination of sedative and non-sedative H1-antihistamines with remarkable improvement of the symptoms (SCORMA 39.2). Urticaria pigmentosa is rare. Limited definitive data has been obtained regarding the prevalence and clinical profile of this disease. Urticaria pigmentosa most commonly affects children and more than 50% of cases occur before the age of 2 years. The prognosis of UP depends on patient's age, disease severity, and clinical subtype. In 50-60% of cases will improve during adolescence.

Key words
Cutaneous mastocytosis; Mast cell; Darier's sign.

Introduction

Mastocytosis is a genetic disorder which characterized by an abnormal increase of mast cells and their cell mediators release in the skin and other tissues. The incidence of mastocytosis is 1:10,000 to 1:30,000 including in children and adults. Mastocytosis has been classified by World Health Organization (WHO) into: cutaneous and systemic mastocytosis.[1]

Urticaria pigmentosa (UP) is a form of cutaneous mastocytosis. It is commonly affect children. The onset of childhood mastocytosis usually appear during neonate, infancy (<6-month-old) and children's age (6 months – 16 years). About 60 – 80% occurs before 1 year-old and internal organ involvement is rare. The prevalence of male and female is 1:1.[2]

Urticaria pigmentosa presents as pruritic brownish macules, patches or papules with a size of 1 – 2.5 cm. Lesions are usually found on the trunk, however lesions on the face, scalp, palms and soles were also reported. The cause of urticaria pigmentosa is still uncertain. It is reported that UP appears due to mutation in the c-kit gene. The diagnosis is established through clinical and histopathologic examination. The mainstay of UP management is to prevent precipitating factors and to control disease activity with topical and systemic therapy.[2]

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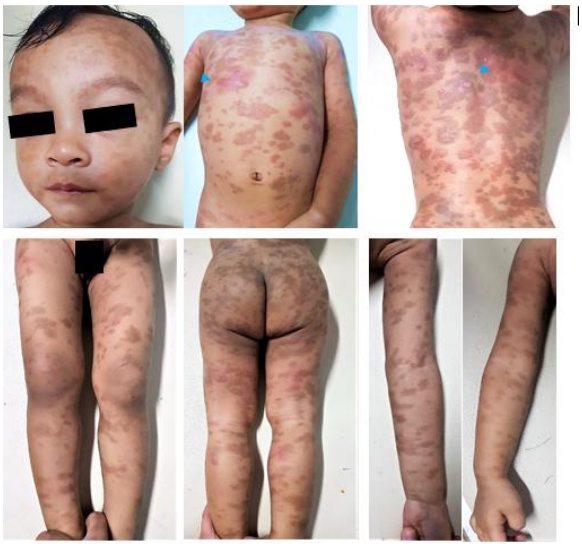

Figure 1 Clinical photo of the patient showing generalized hyperpigmented macules, patches, and multiple erythematous wheal (blue arrow).

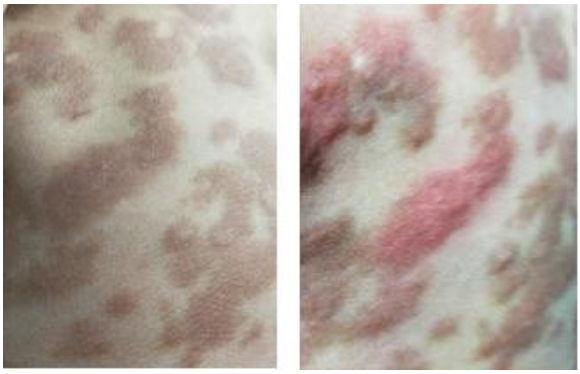

Figure 2 (A) Hyperpigmented patches on patient's back. (B) Positive darier's sign was showed by the appearance of erythematous wheal after gently rubbing on the hyperpigmented patches.

This report aimed to describe the clinical features and histopathologic characteristics of UP patient seen in a tertiary hospital in Indonesia. It also aimed to depict the disease severity evaluation, management strategy and clinical outcome of the patient which may lead to early recognition of UP with appropriate management. It can also serve as a basis for further studies on mastocytosis.

Case report

A 1-year-old boy with complaints of reddish bumps associated with pruritus on the face, neck, chest, back, neck and both upper and lower extremities since 7 months prior to consult. Pruritus sensation often caused sleeping disturbance particularly at night. Lesions appear if triggered by friction, scratching and hot weather then some lesions evolved into blister which then dried up and healed, leaving brownish patches. Patient had a history of episodic fever since the age of 7 months old associated with the eruption of the erythematous bumps. Fever usually resolved with oral paracetamol. History of triggering food was absent.

History of flushing, nausea, diarrhea, anorexia, difficulty of breath, or allergic reaction were denied. Patient's mother denied history of applying herbal medications; contact with harsh chemical on patient's skin; anti-inflammatory nor cough remedies intake on patient.

The patient was the first child of a primigravida mother. He was born at term and normal birth weight without maternal complication. Past medical history and family medical history were non-contributory.

On physical examination, patient was active without developmental delay. He had a normal nutritional status and vital signs. General physical examination showed no enlarged lymph nodes, enlarged liver, enlarged spleen, nor bone deformities.

Dermatological examination revealed a generalized, well-defined, irregularly shaped hyperpigmented macules, patches, more than 100 in with a size ranged from 0.2 x 0.2 cm to 5x3 cm. There was also appearance of erythematous wheal on several part of the hyperpigmented patches **(Figure 1)**. Darier's sign was positive **(Figure 2)**. Dermoscopy examination using a polarized dermoscopy showed a dark brown reticular pigment network **(Figure 3)**. Children's dermatology life quality

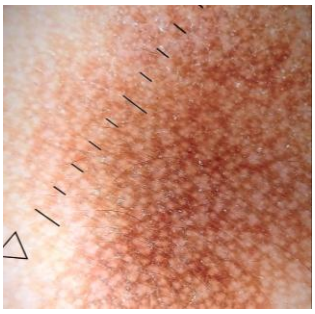

Figure 3 Polarized dermatoscopy (Heine DELTA One) on the hyperpigmented patch showed dark brown reticular pigment network (blue arrow).

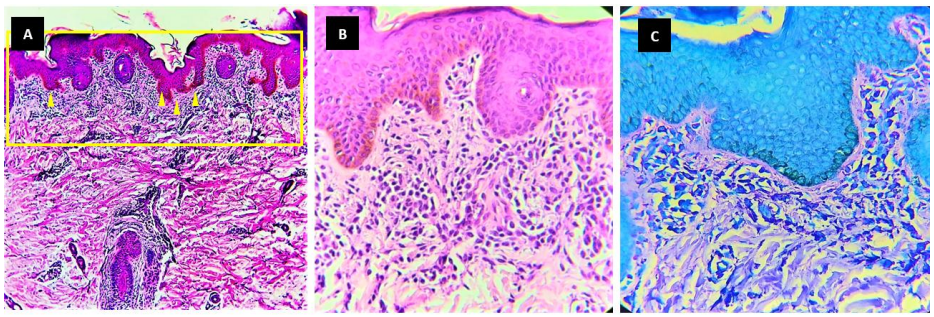

Figure 4 Histopathological examination with Hematoxylin & Eosin. (A) On the scanning view (100x) there were appearance of melanin pigment in the basal layer (yellow triangle) and clusters of inflammatory cells (yellow squares) in the dermal papillae. (B) The dermis revealed clusters of mast cells with eosinophilic cytoplasm, large and pale nuclei (400x) which stained positively with Giemsa stain (C) as purplish granules.

index (CDLQI) was 14 (very large effect) and SCORMA was 53.4.

Laboratory examination of hematology and liver function were within normal value. Patient was also referred to the pediatric department to rule out any possibility of systemic mastocytosis (SM). Referral to pediatric department signify the absence of internal organ involvement in this patient. Histopathology examination revealed several features which confirmed the diagnosis of cutaneous mastocytosis **(Figure 4)**.

Management for this patient was done by symptomatic approach, patient's family education, and avoidance of triggering factor. Patient was prescribed with cetirizine 0.3 mg/kg/day combined with chlorpheniramine maleate 1 mg once a day as needed; topical moisturizing cream containing urea 10%; and topical mometasone furoate 0.1% cream applied on the erythematous wheal not for more than 8 weeks. Patient's SCORMA index was upon follow-up was decreased into 39.2. Patient's family was also explained to avoid the triggering factors and possibility of relapse by the time until the patient reach puberty. Patient's prognosis is good.

Discussion

Mastocytosis is a group of diseases characterized by abnormal infiltration of mast cells in the skin and sometimes other organs and the simultaneous release of chemical mediators by these cells.[3] The organ most often involved in mastocytosis is the skin. Cutaneous mastocytosis (CM) is classified according to clinical presentation and by the onset of the disease. CM is a relatively unusual condition in pediatric dermatology. Its prevalence in the united states ranges from 1:1000 to 1:8000 dermatology patients.[4] Indonesian data regarding UP prevalence is scarce. One published data of UP cases during 2015 to 2019 in Pediatric Dermatology Division, Dr. Cipto Mangunkusumo National General Hospital reported 12 new cases of UP during that period.[5] In our institution, there is absent of published report of UP case.

Urticaria pigmentosa is one of the most common types of CM. There is lack of definitive data to obtained regarding the exact prevalence of this disease. A retrospective study of 180 pediatric patients with mastocytosis from Israel of which 65% were diagnosed with UP (117 cases). Urticaria pigmentosa distribution was found in trunk and extremities. Symptoms associated with UP include asthma (10.3%), flushing 12.8%, fever 1.7% and abdominal pain at 2%.[6] Urticaria pigmentosa is clinically easily

recognizable by the presence of itching. The clinical picture of urticaria pigmentosa is macule, plaques or papules that can appear as hundreds of skin lesions, round or oval in shape with a well-defined border, reddish or pale in color, measuring 1-2 cm which will then leave brownish patches while the common urticaria generally do not leave brownish patches. Urticaria pigmentosa is rarely found on hairy skin, face, palms, and feet.[2]

Urticaria pigmentosa commonly appears during infancy aged one year.[1] In this case, the patient is a 1-year-old child with an early lesion that appeared when the patient was 5 months old. The lesions initially appear as erythematous wheal-like papules and plaques on his trunk which then resolved by leaving hyperpigmentation.

Systemic symptoms that can appear include hepatosplenomegaly, flushing, peptic ulcer, fever, weight loss, night sweats, bone pain, and mental disorders. These symptoms can arise if there are stimuli such as heat, excessive activity, local trauma, or certain medications.[1] In this case, patient experienced pruritus and a history of wheal which then leaves brownish patches. These symptoms usually triggered by friction and heat. Patient also experienced an episodic fever associated with the appearance of erythematous wheal.

Darier's sign is a pathognomonic sign of UP with occurrence of a wheal within a few minutes after mild friction on the lesional skin without any spread to the normal surrounding skin. Although darier's sign is a specific clinical manifestation, a negative darier's sign does not rule out mastocytosis because its positivity rate may vary, ranged from 88% to 92% of cases.[1] Patient in this case showed a positive darier's sign.

Urticaria pigmentosa is a non-melanocyte disease that shows the picture of pigment network accentuation in dermoscopy. Factors secreted by mast cells induce melanocyte proliferation and melanin production resulting in excessive pigment tissue seen in dermoscopy. Nirmal B, *et al.* (2019) Reported that the dermoscopy feature of reticular pigment network was darker in children with positive darier's sign.[7] Dermoscopy from the brownish patches in this patient showed dark brown reticular pigment network which correlate with increase melanin deposition in the epidermal basal layer.

The diagnosis of urticaria pigmentosa is defined based on clinical history and physical examination, which showed a positive darier's sign. The criterion of CM diagnosis is not well established. Cutaneous mastocytosis is commonly diagnosed by physical examination of typical skin lesions as its major criteria, especially in children. In addition to the major criteria, 2 minor criteria are usually occur. The first criteria is the histologic finding of increased number of dermal mast cells in lesional skin. Most patients showed at least a 4-fold increase of dermal mast cells. The second minor criteria is detection of a cutaneous codon 816-KIT mutation.[8] Patient in this case had a typical skin lesion and histopathologic feature which fulfilled the diagnostic criteria of CM.

In UP, the number of mast cells in the dermal papillae is increasing but the number has not been standardized. Mast cells can also infiltrate around blood vessels, and sometimes eosinophils can be encountered. Basic staining such as Giemsa and toluidine blue can be used to see the presence of mast cells more clearly.[2] In this case, histopathological results are obtained from the lesional skin. The epidermis showed the presence of basal melanocyte pigment. The dermis revealed an inflammatory infiltrate consisting of mast cells with a granulated cytoplasmic morphology and a spherical nucleus

which highlighted by giemsa staining. This patient's histopathologic finding is appropriate for urticaria pigmentosa.

Laboratory examinations such as: complete hematology, blood chemistry, liver function can guide the diagnosis to rule out internal organ involvement. Normal laboratory value is usually obtained in CM, but follow-up is required every 6-12 months. Abnormal tests or lymphadenopathy or hepatosplenomegaly on physical examination may indicate systemic mastocytosis (SM). The child should be further evaluated by abdominal ultrasound or computed tomography (for hepatosplenomegaly, lymphadenopathy) and bone marrow biopsy.[1] Patients in this case report showed normal hematological examination as well as liver function test.

Urinary histamine levels may be useful for identifying children at risk of gastrointestinal ulceration. Urinary histamine metabolites also correlate with bone marrow involvement. Recent study reports that serum tryptase levels, a serum marker can help distinguish between SM and CM and also useful to monitor therapeutic response. Serum tryptase levels are usually normal in CM. However, cases of CM with elevated tryptase level has also been reported.[4] Patient in this report did not experience gastro-intestinal symptom nor hematologic abnormality. Urine histamine levels and serum tryptase levels were not performed due to the unavailability of both tests at our facility.

A new method for evaluating the extent of the disease, the activity of skin lesions and the psychological impact caused by the cosmetic aspects of the skin, known as the mastocytosis assessment index (SCORMA). It provides a reference about point of view for doctors and patients.[4,9] The score of SCORMA is between 5.2 to 100 and the higher the SCORMA value indicates a higher degree of severity.[9] In a study by Heide R, *et al.* (2008) reported that there was a positive correlation between the SCORMA Index and serum tryptase levels, indicating the value of the SCORMA Index in the assessment of mastocytosis with skin involvement.[9] However further study need to be conducted to establish the degree of CM severity and to determine certain SCORMA index which corelate to certain serum tryptase level. Baseline SCORMA in our patient was 53.4. In this case, SCORMA was used to assess the disease progression and treatment response.

The management of UP consists of 3 aspects, i.e. counseling, avoiding precipitating factors that can stimulate mast cell degranulation, as well as therapeutic aspects. In the counseling aspect, education to the patient's parents about the disease and disease history is very important because urticaria pigmentosa is benign and only requires symptomatic treatment. There is possibility of spontaneous resolution before puberty. Patient's family should be informed about the factors that can stimulate the rapid release of mast cell mediators. These factors include bathing with hot water, insect bites, and physical trauma. In addition, cough medicines containing dextromethorphan or codeine are potential to activate mast cells.[2]

H1 antihistamines have been shown to be useful in reducing pruritus, flushing, urticaria and tachycardia. Sedative and non-sedative antihistamines can be used in combination. Combined treatment with antihistamines H1 and H2 has also been shown to be effective in some cases to control pruritus and wheal.[2] Patient was treated with a combination of sedative and non-sedative H1 antihistamines. A decrease in SCORMA was obtained with combination therapy. Topical corticosteroids can reduce skin symptoms and cause cosmetic improvements.

Nevertheless, these drugs should be prescribed only for short term.[10]

In children, CM presented as a benign, self-limitted clinical course and rarely remains active during adolescence nor poses a risk of systemic disease in adulthood. The age of onset of UP in children has prognostic implications. Urticaria pigmentosa starting before the age of 10 years experiences partial or complete remission at puberty in 55-90% of patients.[4,11] In this case, the patient initially developed an UP lesion before the age of 1 year. Therefore, our patients are expected to have a favorable prognosis.

Conclusion

Clinical feature, positive darier's sign and typical histopathological examination confirm the diagnosis urticaria pigmentosa. Therapy with a combination of sedative and non-sedative H1 antihistamines may reduce the symptoms of pruritus and the quality of the patient's sleep. Clinical improvement in patients is evaluated based on a decrease in SCORMA. Since this is a form of CM without systemic involvement, the prognosis is good and it can be expected that the lesion will heal over the few succeeding years.

References

1. Sandru F, Petca RC, Costescu M, *et al*. Cutaneous mastocytosis in childhood—update from the literature. *J Clin Med*. 2021;**10(7)**:1474.
2. Castells M, Metcalfe DD, Escribano L. Diagnosis and treatment of cutaneous mastocytosis in children: Practical recommendations. *Am J Clin Dermatol*. 2011;**12(4)**:259–70.
3. Solanki PK, Bhide V, Gadage V, Kulkarni V, Patki A. Cutaneous mastocytosis in an infant: Case report and clinicopathological correlation. *Glob J Med Clin Case Rep*. 2021;**8(3)**:108–111.
4. Kiszewski AE, Durán-McKinster C, Orozco-Covarrubias L, Gutiérrez-Castrellón P, Ruiz-Maldonado R. Cutaneous mastocytosis in children: A children analysis of 71 cases. *J Eur Acad Dermatol Venereol*. 2004;**18(3)**:285–290.
5. Anissa L, Mahri S, Astriningrum R, Agustin T, Rihatmadja R, Rahmayunita G. Bullous Urticaria Pigmentosa in an Infant: A Rare Form of Bullous Disorder. In Proceedings of the 2nd International Conference on Tropical Medicine and Infectious Disease (ICTROMI 2019), 267–271 (2020). doi:10.5220/0009986302670271
6. Ben-Amitai D, Metzker A, Cohen H. Pediatric cutaneous mastocytosis: a review of 180 patients. *Isr Med Assoc J*. 2005;**7(5)**:320–2.
7. Nirmal B, Krishnaram SA, Muthu Y, Rajagopal P. Dermatoscopy of Urticaria Pigmentosa with and without Darier's Sign in Skin of Colour. *Indian Dermatol Online J*. 2019;**28(10)**:577–9.
8. Hartmann K, Escribano L, Grattan C, *et al*. Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; The American Academy of Allergy, Asthma & Immunology; And the European Academy of Allergology and Clinical Immunology. *J Allergy Clin Immunol*. 2016;**137(1)**:35–45.
9. Heide R, Van Doorn K, Mulder PG, *et al*. Serum tryptase and SCORMA (SCORing MAstocytosis) Index as disease severity parameters in childhood and adult cutaneous mastocytosis. *Clin Exp Dermatol*. 2009;**34(4)**:462–8.
10. Czarny J, Lange M, Ługowska-umer H, Nowicki RJ. Cutaneous mastocytosis treatment : strategies, limitations and perspectives. *Postep Dermatol Alergol*. 2018;**35(6)**:541–5.
11. Azaña JM, Torrelo A, Mediero IG, Zambrano A. Urticaria Pigmentosa: A Review of 67 Pediatric Cases. *Pediatr Dermatol*. 1994;**11(2)**:102–6.